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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/006,909 | 12/06/2001 | Jay Keasling | 2000-0007 | 1524 |

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BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

| EXAMINER | |
|---|---|
| FRONDA, CHRISTIAN L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 12/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/006,909 | KEASLING ET AL. | |
| | Examiner | Art Unit | |
| | Christian L. Fronda | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-21 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-8,10,12-21 and 23* is/are rejected.

7)☒ Claim(s) *5,9 and 11* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Claims 1-21 and 23 are pending and under consideration in this Office Action.

2. The rejection of claims 1-4, 6-8, 10, 12-21, and 23 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn in view of applicants' amendments and arguments filed 10/06/2005

3. The rejection of claims 1-4, 6-8, 10, 12-21, and 23 under 35 U.S.C. 103(a) has been withdrawn in view of applicants' amendments and arguments filed 10/06/2005. The examiner agrees with applicants that the reference of Takagi et al. does not teach condensing two molecules of acetyl-CoA to acetoacetyl-CoA, and that the references of Wang et al., Balbas et al., and Fujiaski et al. do not correct the deficiency of Takagi et al. However, a new rejection under 35 U.S.C. 103(a) for these claims is stated below.

### *Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 15-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 recites the phrase "wherein the isopentenyl pyrophosphate is further modified to provide an isoprenoid" renders the claim vague and indefinite. The metes and bounds of the claim are not clear since the claim does not specifically recite how the isopentenyl pyrophosphate is modified to provide the recited products. Claims 16-21 which depend from claim 15 is also rejected because they do not correct the defect of claim 15.

***Claim Rejections - 35 U.S.C. § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 3, 4, 6-8, 10, 12-14, 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takagi et al. (J Bacteriol. 2000 Aug;182(15):4153-7; reference of record) in view of Hiser et al. (J Biol Chem. 1994 Dec 16;269(50):31383-9, and Accession L20428; PTO892) and Wang et al. (Accession AF119715. 22-April-1999; reference of record).

Takagi et al. teach a method comprising the steps of culturing a transformed *E. coli* JM109 strain (a prokaryote that does not normally synthesize isopentenyl pyrophosphate via a mevalonate pathway) harboring a gene cluster for the mevalonate pathway from *Streptomyces* sp. Strain CL190 that is contained in the plasmid pUMV19, where the gene cluster encodes the following enzymes of the mevalonate pathway: mevalonate kinase, diphosphomevalonate decarboxylase, phosphomevalonate kinase, and HMG-CoA synthase (see entire publication, especially pp. 4154-4156).

Takagi et al. does not teach that the said *E. coli* JM109 strain is transformed with a nucleic acids encoding an acetoacetyl-CoA thiolase, which condenses two molecules of acetyl-CoA to acetoacetyl-CoA , and an isopentenyl pyrophosphate isomerase.

Hiser et al. teach a nucleic acid from *Saccharomyces cerevisiae* encoding an acetoacetyl-CoA thiolase that condenses two molecules of acetyl-CoA to acetoacetyl-CoA (see entire publication especially abstract and *Results* section on pp.31384-31387, and Accession L20428).

Wang et al. teach a nucleic acid encoding isopentenyl pyrophosphate isomerase (see Accession AF119715).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Takagi et al. such that the said *E. coli* JM109 strain is transformed with [the nucleic acid encoding an acetoacetyl-CoA thiolase that condenses two molecules of acetyl-CoA to acetoacetyl-CoA as taught by Hiser et al. and the nucleic acid taught by Wang et

al. encoding isopentenyl pyrophosphate isomerase. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to have a beneficial culturing method that produces iopentenyl pyrophosphate (IPP). The limitations of claims 6 and 8 are within purview of one of ordinary skill in the art since it is well known that separate vectors for specific nucleic acids encoding enzymes are used for expression of enzymes in host cells.

Since the nucleic acids taught by Takagi et al. and Wang et al. encode the enzymes recited in claim 10, the Examiner takes the position that the encoded enzymes have the same activity and amino acid sequences of the recited enzymes from *Ralstonia, Saccharomyces, Escherichia coli, Blattella, Sulfologus,* and/or *Haloferax.* Since the Patent Office does not have the facilities for examining and comparing the recited nucleic acids encoding the recited enzymes to the prior art nucleic acids and their encoded enzymes, the burden is on applicant to show that the prior art nucleic acids are different from the recited nucleic acids. See *In re Best,* 562 F.2d 1252, 195 USPQ 430(CCPA 1977).

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

8. Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Takagi et al. in view of Hiser et al. and Wang et al. as applied to claims 1, 3, 4, 6-8, 10, 12-14, 23 above; and further in view of Balbas et al. (Gene. 1996 Jun 12;172(1):65-9; reference of record).

Balbas et al. teach the pBRINT family of plasmids for chromosomal integration of cloned DNA into the *E. coli* genome and method for integration of cloned DNA into the *E.coli* chromosome using these plasmids (see entire publication).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the modified method of Takagi et al. such that the nucleic acids encoding the mevalonate pathway enzymes are cloned into the pBRINT family of plasmids taught by Balbas et al., which are then used in turn to integrate the nucleic acids into the said *E. coli* JM109 strain using the method taught by Balbas et al. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

9. Claims 15-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takagi et al. in view of Hiser et al. and Wang et al. as applied to claims 1, 3, 4, 6-8, 10, 12-14, 23 above; and further in view of Fujisaki et al. (J Biochem (Tokyo). 1986 May;99(5):1327-37. ABSTRACT; reference of record).

Fujisaki et al. teach that isopentenyl pyrophosphate isomerase, farnesyl pyrophosphate synthetase, octaprenyl pyrophosphate synthetase and undecaprenyl pyrophosphate synthetase are four enzymes in *E.coli* that in combination ensures the *in vivo* synthesis of long-chain isoprenoids in *E.coli* (see abstract).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to further modify the modified method of Takagi et al. such that the isoprenoid precursor is reacted with the enzymes taught by Fujisaki et al. for the purpose of having a method that produces isoprenoids. In absence of facts to the contrary, the Examiner takes the position that the modified method of Takagi et al. would inherently produce the recited isoprenoids since the modified method of Takagi et al. comprises all recited the method steps. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

## ***Conclusion***

10. No claims are allowed.

11. Claims 5, 9, and 11 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

13. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CLF